REMARKS

Claims 1-40 were present in the application as filed. In a Preliminary Amendment, claims 1-40 were canceled and new claims 41-60 were added. In response to a restriction requirement, Applicants elected with traverse Group I, claims 41-44, 49-50 and 55-56, drawn to controlled release pharmaceutical compositions containing descarboethoxyloratadine (hereafter, "DCL") and lactose-free carrier.

In the Non-Final Office Action dated November 5, 2003, the Examiner rejected claims 41-45, 49-51 and 55-57, agreed to additionally examine claims of Group II, claims 45, 49, 51, 55 and 57, drawn to controlled release pharmaceutical compositions containing DCL and a lactose-free carrier, in combination with an analgesic or a decongestant, and pursuant to restriction requirement withdrew claims 46-48, 52-54 and 58-60 from further consideration. Applicants filed a Response to Non-Final Office Action traversing the rejection.

In the Final Office Action dated October 8, 2005 (hereafter "Office Action") the Examiner rejected claims 41-45, 49-51 and 55-57. A Notice of Appeal was filed on January 11, 2005.

Presently, the Applicants are submitting a Request for Continued Examination and make of record additional references. The Examiner's rejections are traversed below. The claims now pending in the application are: 41-60.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 41-45, 49-51 and 55-57 under 35 U.S.C. §103(a) as being unpatentable over Villani et al. (US Pat. No. 4,659,716) and Aberg et al. (US Pat. No. 5,731,319), in view of Blaug et al.,[1] Hartauer et al.,[2] the Handbook of Pharmaceutical Excipients,[3] and Remington's Pharmaceutical Sciences.[4]

The Examiner stated that Villani et al., and Aberg et al. teach DCL in combination with pharmaceutical carriers and excipients. Furthermore, the Examiner asserted that "Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients teach various amine compounds, in high temperature and humidity situations reacting with various sugars, producing a concomitant reduction in active ingredients levels" (Office Action, p. 4, first full paragraph). Based on this, the Examiner concluded that "[t]he skilled artisan possessing these teachings would have been motivated to eliminate lactose and sugars from those medicaments containing amine active ingredients, such as those herein claimed." (*Id.*)

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations (*see*, MPEP § 2143).

The Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of obviousness. In the "Response to Arguments" section of the Office Action, the Examiner is requiring showing of unexpected benefits of the claimed invention. However, the Applicants

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[1] Interaction of Dextroamphetamine Sulfate with Spray-Dried Lactose, J. of Pharma. Sciences, 61 (11), pp. 1770-1775 (1972).
[2] A Comparison of Diffuse Reflectance FT-IR Spectroscopy and DSC in the Characterization of a Drug-Excipient Interaction, Drug. Dev. and Ind. Pharma., 17 (4), pp. 617-630 (1991).
[3] Wade et al., 2nd edition, American Pharma. Assoc. & the Pharma. Press, Royal Pharma. Society of G. Britain, pp. 257-259 (1994).
[4] Genaro et al., 17th edition, Philadelphia College of Pharmacy and Science, pp. 1633-1638 (1985).

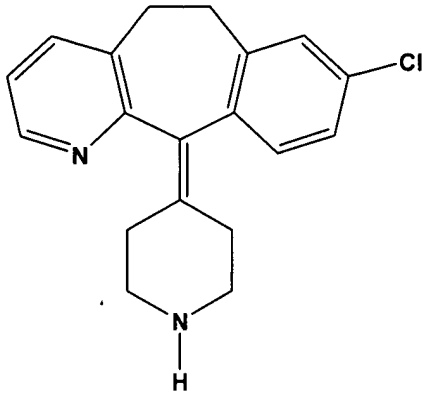
respectfully assert that a showing of unexpected advantages or superior properties is required **only** if the *prima facie* case of obviousness has been made. (*See, e.g.*, MPEP §§ 716.02(c) and (e), and 2144.09), It is Applicants' position, supported by previously made of record Declaration of Dr. Sharon M. Laughlin (hereafter, "Declaration"), that the cited by Examiner references do not suggest or motivate presently claimed invention. Therefore, the cited references are insufficient to form a basis for an obviousness rejection, the *prima facie* case of obviousness is not established, and the requirement to show unexpected benefits is not applicable.

Specifically, the cited secondary references of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients, do not suggest or motivate to modify prior art DCL formulations by intentionally excluding lactose from such formulations. This is due to the fact that these secondary references do not teach or suggest that secondary amines, such as DCL, are reactive with lactose.

The Declaration sheds light on the scope of the teaching afforded to a person of skill in the art by the secondary references of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients.

The Declaration states that a person of skill in the art, would take the disclosures of Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients as teaching that a primary amine may react with lactose. However, from the teachings of these references, there would be an expectation that a secondary amine, such as DCL, would not interact with lactose and that lactose-containing DCL compositions would be stable.

As explained in the Declaration, a primary amine is a compound that has a nitrogen atom (N) bound by a covalent bond to only one carbon (C) atom. A secondary amine is a compound that has a nitrogen atom bound by a covalent bond to two carbon atoms. The DCL is a secondary amine since each of its two nitrogen atoms are bound to two carbons as shown below:



Primary and secondary amines represent two distinct species of amine compounds.

The Declaration states that Blaug et al., in the introductory paragraphs, provides a recitation of early thoughts with respect to the incompatibility of amines (with disregard as to species) and lactose. The early investigators recognized that tablets containing amine salts and lactose discolored (turned brown) slowly on storage and concluded that the discoloration was a result of liberation of free amine by basic lubricants in the formulation. In 1965, however, Duvall *et al.* concluded that browning did not depend upon liberation of free amine, but that the lactose/amine interaction was predominantly a *primary amine*-carbonyl type of reaction. The investigation conducted by Blaug (1972) confirmed the conclusions of Duvall et al. that the reaction is "a Schiff base-type [reaction] involving the primary amine and the carbonyl group of the sugar." (page 1772, col. 2 and page 1774, col. 1). Thus, Blaug et al. shows that while the early theory for the browning reaction did not account for amine species, subsequent discoveries did, and concludes that lactose/amine incompatibility was the result of an interaction between lactose and a primary amine. Therefore, from the disclosure in Blaug et al., one of skill in the art would not expect a secondary amine, such as DCL, to be reactive with lactose.

Furthermore, the Declaration states that Hartauer et al. also teaches that the incompatibility between lactose and amines arose as a result of an interaction between lactose and *primary* amines. Hartauer et al. tested aminophylline, a composition comprised of two molecules of theophylline and one molecule of ethylenediamine. This study compared reactivity of lactose with theophylline, a secondary amine, and ethylenediamine, a primary amine.

Hartauer et al. found that while theophylline, a secondary amine, did not interact with lactose, ethylenediamine, a primary amine, did. Thus, Hartauer et al teaches that the primary amines are reactive with lactose while the secondary amines are not reactive with lactose. Therefore, the disclosure in Hartauer et al., would make one of skill in the art expect that a secondary amine, such as DCL, would not be reactive with lactose.

Similarly, as stated in the Declaration, the Handbook of Pharmaceutical Excipients teaches on page 257 that "a Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown-colored products." Thus, the Handbook of Pharmaceutical Excipients does not teach incompatibility of lactose with secondary amines.

According to the Declaration, prior to Applicants discovery, DCL was routinely formulated with lactose (*see, e.g.*, Aberg et al. US Pat No. 5,731,319, Examples 7 & 8). This fact demonstrates that there was no recognition of the fact that DCL, a secondary amine, is incompatible with lactose. Moreover, another secondary amine, astemizole, was commercially available from 1988 until 1999 as HISMANAL® tablets (Janssen Pharmaceutica, Inc.) which, according to the *Physician's Desk Reference*, 50th Ed., Medical Economics Co., Montvale, NJ, p. 1293 (1996), contained in each tablet, 10 mg astemizole and lactose in addition to other ingredients. HISMANAL® was removed from the market in 1999 due to safety concerns and not due to astemizole's incompatibility with lactose.

Therefore, the Declaration concludes that Blaug et al., Hartauer et al., and the Handbook of Pharmaceutical Excipients do not teach a person of skill in the art that a secondary amine such as DCL may react with lactose.

As evidenced by the Declaration, the state of the art at the time of the invention was such that the person of skill would expect that a secondary amine such as DCL would not interact with lactose and that lactose-containing DCL compositions would be stable. Thus, Applicants' discovery of the incompatibility of lactose and DCL was therefore unexpected and surprising.

The Examiner stated that he found the Declaration unconvincing. The Examiner appeared to question credibility of the declarant, Dr. Sharon M. Laughlin, by pointing out that he is "unaware a Doctor of Philosophy degree in Pharmacy was granted anywhere in the United States" (Office Action, page 6, last paragraph). If the Examiner wishes to see proof of the declarant's credentials, such proof could be presented upon request.

The Examiner also cited Remington's Pharmaceutical Sciences reference as teaching coating of the dosage form with an inert coating agent. This reference lacks relevance since, as demonstrated above, the prior art did not recognize the fact that lactose represents a non-inert coating agent for DCL formulations.

Furthermore, the Aplicants respectfully present that a conclusion of obviousness cannot stem from improper hindsight reasoning (*see* MPEP § 2145). "Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but **so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure**, such a reconstruction is proper." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971) (emphasis added).

The Declaration presented evidence of the knowledge which was within the level of skill in the art at the time the claimed invention was made. This evidence demonstrated that the cited by the Examiner prior art did not suggest or motivate the presently claimed invention. Therefore, the Applicant's respectfully assert the Examiner's conclusions of obviousness are based on impermissible hindsight gleaned from Applicants' disclosure.

For all of the above reasons, the Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of obviousness. Consequently, the Applicants respectfully submit that clams 41-45, 49-51 and 55-57 are not obvious.

Request for Continued Examination and Information Disclosure Statement

An Information Disclosure Statement is being filed concurrently with the present Response and Request for Continued Examination (RCE) in order to make of record certain additional references of which the Applicants have become aware.

The Applicants, out of an overabundance of caution, and in light of recent case law interpretation of the "material to patentability" requirement of prior art as it was applied in *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 66 USPQ2d 1481 (Fed. Cir. 2003) and related cases, wish to make of record the Wirth *et al.* reference, which became public **after** the priority dates of the present application.

The Wirth *et al.* reference states that formulations of fluoxetine HCl, a secondary amine, containing lactose as an excipient, are less stable than formulations of fluoxetine HCl with starch. The instability of formulations containing lactose is disclosed to be due to Maillard reaction between the fluoxetine HCl and lactose. The abstract of Wirth *et al.* reference concludes that:

> "The main conclusion is that drugs which are secondary amines (not just primary amines as sometimes reported) undergo the Maillard reaction with lactose under pharmaceutically relevant conditions. This finding should be considered during the selection of excipients and stability protocols for drugs which are secondary amines of their salts, just as it currently is for primary amines."

The Applicants argued in the past that the presently claimed compositions are patentable due to non-obviousness of the lactose free DCL compositions. Since both DCL and fluoxetine are secondary amines, the Wirth *et al.* article presents conclusions of incompatability between secondary amines and lactose that are similar to issues previously argued by the Applicants.

However, the Applicants note that the Wirth *et al.* reference bears an earliest date of **December 15, 1997** for publication of the abstract in *Advance ACS Abstracts*. The complete reference was published on the web on **January 2, 1998** (*see* Wirth *et al.*, p.31). Thus, the Wirth

et al. reference has an earliest publication date that is **later** than the priority dates of the present application, which are **February 7, 1997** (USSN: 60/037,325), **April 30, 1997** (USSN: 60/045,184), and **July 21, 1997** (USSN: 60/053,050). Therefore, the Wirth *et al.* reference does not qualify as relevant prior art. If anything, the conclusions reported in Wirth *et al.* support Applicants' past assertions that incompatibility between secondary amines and lactose in pharmaceutical formulations was not recognized by persons of skill in the art at the priority dates of filing of the present application.

It should be further noted that the Wirth *et al.* reference on page 31, bottom of first column and beginning of second column, states that:

> "Reducing carbohydrates such as glucose, maltose, and lactose are substrates for the Maillard reaction since their cyclic tautomers are in equilibrium with their more reactive aldehyde forms; nonreducing carbohydrates such as mannitol, sucrose, and trehalose are not subject to Maillard reactions. Although early scientists believed that only primary aromatic amines were capable of this reaction, subsequent research has shown that nearly all primary and secondary amines, aromatic or aliphatic, are capable of this reaction.[9]"

The footnote 9 of the above excerpt is a citation of Hodge *et al.* article also being disclosed herein. Hodge *et al.* reports observations of Amadori rearrangement of glycosylamine derivatives. The Amadori rearrangement is a reaction that is known to occur after Maillard reaction has taken place (see disclosed herein references Yaylayan *et al.* and Ellis (cited under footnote 2 in Wirth *et al.*)). However, Hodge *et al.* does not state that secondary amines undergo Maillard reaction with sugars under ambient conditions.

To the contrary, all of the reactions of amines with sugars reported in Hodge *et al.* were performed under conditions that are drastically different from ambient conditions under which solid pharmaceutical formulations of the present invention are stored. One such reaction reported in Hodge *et al.* is disclosed on page 316, second column, second paragraph, is where 1-desoxy-1-dibenzylamino-D-fructose was obtained from D-glucose and dibenzylamine (a secondary amine) on heating in alcoholic solution. Therefore, the above quoted proposition given in Wirth *et al.* for which Hodge *et al.* is cited is not supportive for a conclusion that

Maillard reaction may occur between a secondary amine and lactose under ambient conditions.

> In addition, the Wirth *et al.* reference on page 31, top of second column, states that:
>
> "The impact of these [Maillard] reactions on the stability of pharmaceuticals has also been known for some time and was recently reviewed.[11]"

The footnote 11 of the above excerpt is a citation of Kumar *et al.* chapter from a book entitled "Mailard Reactions in Chemistry, Food, and Helath" which is also disclosed herein. This reference summarizes reports of occurrence of Maillard reaction in formulations containing lactose and drugs with amine functionality.

Applicants carefully reviewed Kumar *et al.* reference and concluded that it does not disclose a single reaction between a secondary amine and lactose under ambient conditions in solid form formulations. On page 21, second paragraph, mention is made of "a reaction between the primary amine of the dextroamphetamine and the carbonyl group of the lactose." On page 22, reactivity of neomycin, a primary amine, and lactose is reported. On page 23, reactivity of sugars with primary amines benzocaine and norphenylephrine hydrochloride is reported. On page 24, instability of a primary amine nystatin is reported.

On page 24 of Kumar *et al.*, second paragraph, mention and citation is made of studies which showed browning of various commercial liquid oral formulations containing sugars and amine drugs. Although specific active ingredients are not mentioned, the reported studies are not relevant since they address reactivity of liquid rather than solid formulations. The same paragraph also mentions unpublished study by Kumar and Banker on instability of amine drugs in solid and liquid formulations containing oxidized celluloses. This study is also not relevant since it addresses reactivity of amine drugs with oxidized celluloses rather than with lactose and from the provided information it is impossible to assess as to whether any secondary amines were used in the unpublished study.

Furthermore, Kumar *et al.* on page 23, first full paragraph, states that when dextrose is used instead of lactose "the browning is predominantly due to a primary amine-carbonyl (Maillard) rection."

Therefore, the Kumar *et al.* reference, similarly to the above-discussed Hodge *et al.* reference, is not supportive for a conclusion that Maillard reaction may occur between a secondary amine and lactose in solid formulations under ambient conditions. To the contrary, the repeated mentioning of reactivity of primary amines with sugars, and exemplification of instabilities of only primary amines, leads to a conclusion that Kumar *et al.* teaches incompatibility only between primary amines and lactose.

No art currently of record and having an effective date earlier than Applicants' priority discloses incompatibility between lactose and secondary amines under ambient conditions in solid form formulations. Therefore, for all of the above reasons, the Applicants respectfully assert patentability of the present invention.

Conclusion

Reconsideration and further examination is respectfully requested.

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone Edward Timmer, Applicants Attorney at (518) 452-5600 so that such issues may be resolved as expeditiously as possible.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

CERTIFICATE OF MAILING

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Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Date of Deposit: March 11, 2005

Edward Timmer
EDWARD TIMMER

Respectfully submitted,

Edward Timmer
EDWARD TIMMER
Attorney for Applicant(s)
Registration No. 46,248

Dated: March 11, 2005

HESLIN ROTHENBERG FARLEY & MESITI, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579